Mutations in the collagen XII gene define a new form of extracellular matrix-related myopathy.


Abstract

Bethlem myopathy (BM) [MIM 158810] is a slowly progressive muscle disease characterized by contractures and proximal weakness, which can be caused by mutations in one of the collagen VI genes (COL6A1, COL6A2 and COL6A3). However, there may be additional causal genes to identify as in ~50% of BM cases no mutations in the COL6 genes are identified. In a cohort of 24 patients with a BM-like phenotype, we first sequenced 12 candidate genes based on their function, including genes for known binding partners of collagen VI, and those enzymes involved in its correct post-translational modification, assembly and secretion. Proceeding to whole-exome sequencing (WES), we identified mutations in the COL12A1 gene, a member of the FACIT collagens (fibril-associated collagens with interrupted triple helices) in five individuals from two families. Both families showed dominant inheritance with a clinical phenotype resembling classical BM. Family 1 had a single-base substitution that led to the replacement of one glycine residue in the triple-helical domain, breaking the Gly-X-Y repeating pattern, and Family 2 had a missense mutation, which created a mutant protein with an unpaired cysteine residue. Abnormality at the protein level was confirmed in both families by the intracellular retention of collagen XII in patient dermal fibroblasts. The mutation in Family 2 leads to the up-regulation of genes associated with the unfolded protein response (UPR) pathway and swollen, dysmorphic rough-ER. We conclude that the spectrum of causative genes in extracellular matrix (ECM)-related myopathies be extended to include COL12A1.

PMID: 24334769 DOI: 10.1093/hmg/ddt637

[Indexed for MEDLINE]
Mutations in the collagen XII gene define a new form of extracellular matrix-related myopathy.